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REVIEW

Soft tissue sarcoma in France in 2015: Epidemiology, classification and organization of clinical care

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Summary Four thousand new cases of soft tissue sarcomas are diagnosed each year in France, 23% of which are localized in the abdomen and pelvis; the treatment of non-metastatic tumor is based on wide surgical resection, the quality of which determines the long-term outcome. To ensure appropriate care, the European Society of Medical Oncology (ESMO) recommends that any patient with an unexplained soft tissue mass (of any size for deep lesions or of >5 cm for superficial lesions) be referred to a specialized center with capacities for multidisciplinary team decision; appropriate imaging should be performed prior to treatment and a percutaneous image-guided needle biopsy should be routinely performed. In France, clinical and pathology networks (NetSarc and RRePS) currently offer patients a structured means to make a systematic diagnosis of soft tissue sarcoma and help to provide access to appropriate treatment in a specialized center.

Introduction

Sarcomas are rare malignant tumors of mesenchymal origin, that arise in connective tissue, in contrast to the more frequent and better-known carcinomas of epithelial origin [1]. Sarcomas have widely diverse pathologies with more than 70 histological subtypes and an ever-Increasing number of molecular subtypes. They may develop at any age including childhood, can occur anywhere anatomically from head to foot, and are of varying aggressiveness, even within the same histological subtype [2,3]. There are three principal kinds of sarcoma corresponding to different clinicopathological entities with individually specific progression, and specifically different management strategies: bone sarcomas, visceral

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sarcomas that develop in a specific organ (the most typical being gastrointestinal stromal tumors [GIST]), and soft tissue sarcomas (STS) arising in connective tissue and extraosseous connective tissue; these represent about 1% of all adult cancers [4—6]. No formal etiology has so far been defined, but several contributing factors have been identified (genetic mutations of the NF1RB1, WRN, p53, and APC genes, which are responsible respectively for type I neurofibromatosis, congenital retinoblastoma, and the syndromes of Li-Fraumeni, Gardner, and Werner) or extrinsic genetic damage (ionizing radiation, exposure to vinyl chloride, dioxin, chlorophenol, and certain viruses) [2—7]. This update aims to clarify recommendations for the diagnostic and therapeutic management of STS, which are infrequently encountered and poorly understood by most visceral surgeons.

Epidemiology

The exact annual incidence of STM is unknown. Several estimates based on retrospective analyses of cancer registries have been attempted [8—17]. These studies all suffer from methodological bias because the registries were set up to collect data based on the organ of origin, an appropriate methodology for the natural history of carcinoma but unsuitable for sarcomas that may arise in any part of the body. This is particularly the case for visceral sarcomas, which tend to be misclassified as digestive cancers based on the organ in which they arise. Adult registries are often separate from pediatric registries. This results in a systematic underestimation of the incidence of STS [8—17]. In addition, when a pathologist who is unfamiliar with these histological types of tumor performs the pathologic analysis, the risk of initial diagnostic error ranges from 10 to 25% [13—17]. The best estimates of incidence available today come from a French study; the authors, fully aware of diagnostic pitfalls, used a less biased methodology based on a systematic prospective re-analysis of all tumor specimens where a formal diagnosis or suspicion of sarcoma had been made, over a period of two years from 158 public and private practice pathologists in the Rhône-Alpes region of France. Tissue specimens were reviewed by two expert pathologists with additional systematic molecular analysis, and all samples were reclassified according to the 2002 WHO classification [18]. After review of 1287 tissue blocks, sarcoma was definitely diagnosed in 748 patients between 2005 and 2007 in an area with a population of about 6 million people. The overall and age-adjusted incidence of sarcoma was estimated at 6.2 and 4.8 cases per 100,000 population per year, respectively. The incidence of STS and visceral sarcoma were respectively 3.6 and 2.0 cases per 100,000 population per year [18]. The overall male to female ratio was 1.1/1, but there was a female preponderance of visceral sarcomas (1.4/1) and a male preponderance for STS (1.3/1). The median age at diagnosis was 60 years, with a range between 0 and 92 years. Eight percent of patients developed sarcoma before the age of 18, and 28% after the age of 70 years. A graphical representation of the evolution according to age of the incidence of STS is shown in Fig. 1. The median size of the lesion was 6 cm, with extremes ranging from 0.3—40 cm. Localization of STS was truncal in 40% of cases (17% thoracic, 9% retroperitoneal, 8% pelvic and 6% abdominal), while 60% of STS were peripheral (49% localized on a limb and 11% on the head and neck). Of the 433 diagnosed cases of STS, 25 (5.8%) arose in irradiated tissues [18].

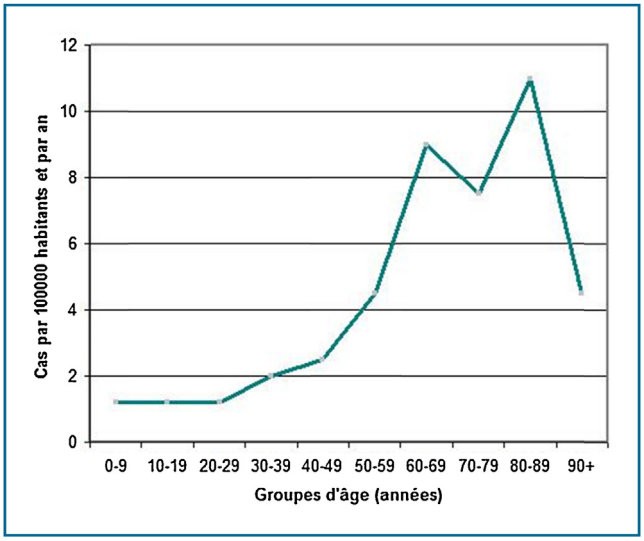

Figure 1. Incidence of soft-tissue sarcoma as a function of age in France. Cases per 100,000 inhabitants per year; age groups (years).

Table 1 Distribution of the principal histologic subtypes of soft-tissue sarcoma in France (2002 WHO Classification).

	n	%
Sarcomas		
Liposarcoma	1092	25.2
Undifferentiated sarcoma	947	21.8
Leiomyosarcoma	741	17.1
Myxofibrosarcoma	252	5.8
Angiosarcoma	219	5.0
Rhabdomyosarcoma	215	5.0
Synovial sarcoma	183	4.2
MPNST	115	2.6
Other	577	13.3
Mesenchymal tumors of intermediate malignancy		
Solitary fibrous tumor	119	
Desmoid tumor	363	

MPNST: malignant peripheral neural sheath tumors.

Extrapolation of these data to the overall French population led the authors to estimate that about 4000 new cases of STS were diagnosed annually in France [18]. An estimation of the distribution of histologic sub-types is illustrated in Table 1, based on the findings of the Network for Pathologic Registry of Sarcomas (RRePS), which has undertaken the systematic histopathologic review of all newly diagnosed cases of sarcoma, GIST, and desmoid tumors [19,20].

Classification of soft tissue sarcomas

Correct classification of STS is imperative from the very beginning of management. It informs and guides the

diagnostic and imaging work-up, and helps to establish the prognosis on which therapeutic management decisions will be based. STS are, by their nature, very heterogeneous and so complex that any classification system has proved inadequate for the individual case. The classification of STS is therefore based on a composite that considers, in addition to general clinical data such as age and primary tumor location, three major factors:

- a complete descriptive histologic analysis according to the latest WHO classification terminology, including molecular sub-typing if necessary;
- an assessment of tumor aggressiveness based on histological grade as defined by the National Federation of Centers for Combatting Cancer (FNCLCC);
- assessment of tumor extension based on the TNM status as defined by the American Joint Cancer Committee (AJCC) and the International Union Against Cancer (UICC) [20].

WHO histological classification

The WHO has recently updated the standard histological classification system for STS [2]. This distinguishes 12 major categories of benign and malignant soft tissue tumors (Table 2a) that are secondarily subdivided into 113 histological subtypes [2]. This is an analogous classification, not based on the local origin of the tumor but rather on attempted identification of the cellular line of differentiation (fat, smooth muscle, striated muscle, cartilage...) taken by the tumor, i.e. based on the aspect of normal tissue that the tumor most closely resembles. This classification is defined by histological arguments based on optical microscopy with the addition of immuno-histochemical analysis. For those sarcomas where no line of differentiation is clearly identifiable, molecular biology allows identification of specific molecular abnormalities that have now been characterized for almost half of sarcomas. These identification markers allow objective and reproducible classification (Table 2b) [21,22]. Sarcomas can currently be classified into five major categories:

- sarcomas with molecular translocations;
- sarcomas with activating mutations;
- sarcomas with inhibitory mutations;
- sarcomas with simple amplifications;
- sarcomas with complex genomic abnormalities [22].

Beyond a strictly nosologic classification, molecular diagnosis of sarcoma has allowed regrouping of microscopically disparate tumors that have identical genetic abnormalities, and differentiation of morphologically identical tumors that present with different molecular abnormalities. They have also provided major hope for therapies targeting the molecular abnormalities with chemotherapeutic agents that currently exist or are in the process of development, similar to the revolutionary results of imatinib therapy for GIST [23].

Table 2a Histologic classification (WHO).

Adipose tumors
Fibroblastic/myofibroblastic tumors
Fibrohistiocytic tumors
Smooth muscle tumors
Peri-angiocytic tumors (perivascular)
Striated muscle tumors
Vascular tumors
Cartilaginous and osseous tumors
GIST (Gastro Intestinal Stromal Tumor)
Nerve sheath tumors
Tumors with uncertain differentiation
Unclassified and undifferentiated sarcomas

Table 2b Soft-tissue sarcomas with defined genetic translocations.

Ewing sarcoma	t(11;22);t(21;22)
Synovial sarcoma	t(X;18)
Alveolar rhabdomyosarcoma	t(2;13);t(1;13)
Myxoid liposarcoma	t(12;16);t(12;22)
Myxoid chondrosarcoma	t(9;22)
Clear-cell sarcoma	t(12;22)
Fibromyxoid sarcoma	t(7;16);t(11;16)
Desmoplastic tumor with small round cells	t(11;22)
Infantile fibrosarcoma	t(12;15)
Alveolar sarcoma of soft tissue	t(X;17)
Inflammatory myofibroblastic tumor	t(2;19);t(1;2)
Angiomatoid histiocytofibroma	t(12;16);t(12;22)

The FNCLCC histologic grade

Histologic classification alone cannot provide sufficient information to predict the clinical course of the disease. Several grading systems for tumor aggressiveness have been proposed since the work of Broders in 1939, but the most precise and reproducible predictor is tumor grade, as defined by the FNCLCC and described by Trojani et al. in 1984 [4,24–28]. This grade is based on an assessment of the initial untreated tumor combining features of tumor differentiation, mitotic index and extent of tumor necrosis to calculate an overall score equivalent to tumor grade, as shown in Tables 3a and 3b. This grade, however, is often much less informative than histologic subtype analysis in the case of some particularly aggressive histological types such as alveolar, epithelioid, clear cell, undifferentiated, round-cell and, rhabdomyosarcoma and Ewing sarcoma.

TNM staging according to the UICC and AJCC

Beyond the intrinsic characteristics of the tumor, diagnostic imaging to determine the spread of the disease can help to complete staging thus enhancing therapeutic decisions. This staging is done using the TNM classification proposed by the UICC and AJCC, which considers the size and extent of the primary tumor (T), regional lymph node involvement (N), the presence of metastasis (M), and tumor grade (G) (Tables 4a and 4b) [29].

Management strategy

Rare cancers pose a particular problem precisely because of their relative scarcity, resulting in failure to diagnose, error in diagnosis, inadequate treatment, lack of treatment guidelines, limited access to complex treatments that are available in only a few centers, and limited access to clinical trials. Organization of care at the national level can help to mitigate these problems. In France, the management of sarcoma is based on two national networks for pathologic diagnosis and clinical treatment, which work co-operatively.

Table 3a FNCLCC histologic grade.

Scores	Description
Tumoral differentiation	
Score 1	Sarcoma resembling normal tissue
Score 2	Sarcoma with clearly defined histologic diagnosis
Score 3	Embryonic sarcoma, synovial sarcoma, epithelioid sarcoma, clear-cell sarcoma, alveolar sarcoma of soft tissue, undifferentiated sarcoma and sarcoma of uncertain histologic type
Mitotic index (1 high-powered field = 0.1734mm^2)	
Score 1	0—9 mitoses per ten high-powered fields
Score 2	10—19 mitoses per ten high-powered fields
Score 3	More than 19 mitoses per ten high-powered fields
Tumoral necrosis	
Score 1	No necrosis
Score 2	Less than 50% tumoral necrosis
Score 3	More than 50% tumoral necrosis

Table 3b FNCLCC histologic grade.

Grade 1	Grade 2	Grade 3
Sum of scores: 2—3	Sum of scores: 4—5	Sum of scores: 6—8

Table 4a TNM staging factors according to the 2010 AJCC/UICC guidelines.

T1	Tumor $\leq$ 5 cm
T1a	Superficial
T1b	Deep
T2	Tumor > 5 cm
T2a	Superficial
T2b	Deep
N0	No lymph node invasion
N1	Lymph node invasion
M0	No distant metastases
M1	Distant metastases

Pathology network

In France, since the early 1980s, a group of pathologists have preferentially worked on the study of connective tissue and soft tissue sarcomas in adults. Thanks to their perseverance, major advances have been achieved, both technically and organizationally. Despite these advances, the diagnosis of STS remains difficult. The risk of initial diagnostic error is 10—25% if a pathologist who is unfamiliar with these histological types carries out the pathologic analysis. Sometimes there are major discrepancies resulting in mistaking a benign lesion for a sarcoma (10% of cases) or mistaking a sarcoma for a benign lesion (4% of cases) [13—17]. Awareness of the consequences that such misdiagnoses might cause led this group of experts to set up a Referral Network for Pathology of Soft Tissue and Visceral sarcomas (RrePS) (http://rreps.sarcomabcb.org/home.htm); this structure was approved in October 2009 by the INCa within the framework of the 2009—2013 National Cancer Plan (Measure 20, Action 20.3) with the aim of ''supporting quality initiatives within the anatomic-cytopathologic community'' and particularly ''in order to enable systematic double-reading of all rare malignant tumors and lymphomas that is essential for diagnostic confirmation'' [30—32]. The objective of this network is to guarantee a second pathologic reading without additional cost for any new case of soft tissue or visceral sarcoma. Other objectives of the network have been to improve the molecular diagnosis of these tumors, to strengthen databases and the collection of tissues to build a national virtual tumor bank, to develop translational research activities both nationally and internationally, to improve the continuing education of pathologists within and outside the network, and to improve patient information directly and by forging strong links to patient associations. In order to perform these functions, the network was organized as a tri-partite National Co-ordinating Center with sites located in Bordeaux, Lyon and Villejuif. Nineteen adjunct expert referral centers were appended to this National Co-ordinating Center, whose distribution is shown in Fig. 2. Since the establishment of RRePS, pathologists have been requested to systematically send slides of any newly diagnosed STS or visceral sarcoma to one of these centers for review by an expert pathologist. During the first two years of its existence, 8251 tissue specimens from 7429 patients have been reviewed by the RRePS. Diagnoses were established for 4589 sarcomas, 1007 GIST, 363 desmoid tumors, 729 tumors of intermediate malignancy, 189 non-mesenchymal malignancies, and 522 benign mesenchymal lesions. The number of sarcomas and GIST that were reviewed corresponded to about 80% of cases expected during this period and were

Table 4b TNM stage according to the 2010 AJCC/UICC guidelines.

Stage IA	T1a	N0	M0	G1
	T1b	N0	M0	G1
Stage IB	T2a	N0	M0	G1
	T2b	N0	M0	G1
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	T1-2	N1	M0	G1-3
Stage IV	T1-2	N0-1	M1	G1-3

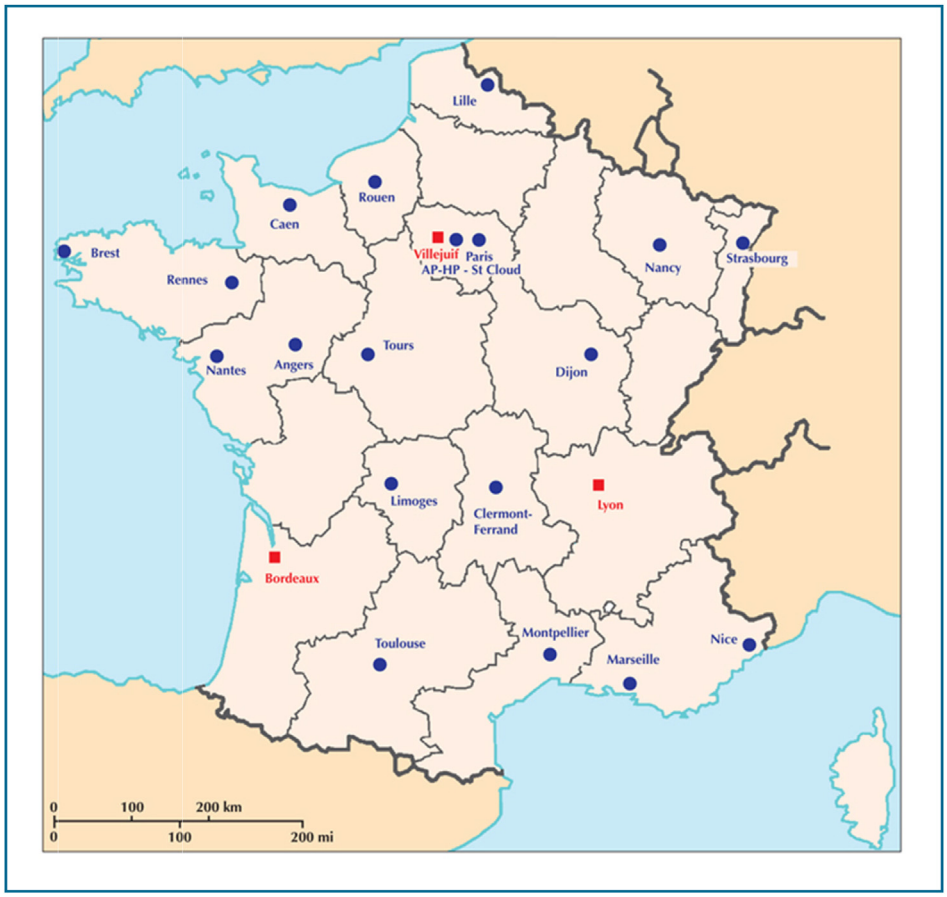

Figure 2. RRePS network (red: coordinating center; blue: referral center).

sent in for review by 1240 of the 1795 active pathologists in France (69%). Re-reading of the slides by RRePS resulted in a change in diagnosis in 25% of cases referred because of diagnostic uncertainty and in 8.5% of cases sent in for systematic pathologic re-reading [19].

Clinical network

In parallel with these pathology initiatives, the organization of the supply of care for adult patients with rare cancers was laid out in measure 23, Action 23.1 of the 2009—2013 National Cancer Action Plan to ''Certify referral centers for rare cancers''. Eight national expert referral centers have been certified so that any patient with a rare cancer can receive treatment in the establishment of their choice, be assured of an expert opinion both for diagnosis and throughout the various stages of their disease, and be eligible for inclusion in clinical trials to facilitate access to innovative therapies. All of these issues are improved by analysis of the database accumulated and collated by each of these centers, through ongoing monitoring of these uncommon diseases. This has resulted in the birth of NetSarc, a Clinical Reference Network for Sarcoma-GIST-Desmoid Tumors (http://netsarc.sarcomabcb.org/home.htm), which pursues five objectives: the definition of recommendations for clinical management; organization of referral resources for patient management; coordination of research; participation in epidemiological surveillance; and organization of a structured care pathway for patients and for physician training and continuing education.

This organization is centered on a tripartite national reference center of expertise located in Paris, Lyon and Bordeaux, with links to a national network of expert centers, operating in coordination with RRePS (Fig. 3). Although the European Society of Medical Oncology (ESMO) has developed specific recommendations that have been adopted as standard by the French networks, a recent prospective study evaluating adherence to these recommendations in the Aquitaine and Midi-Pyrénées regions showed that 20% of patients had undergone operation for deep sarcoma without pre-operative imaging and 48% had no established histological diagnosis at the time of surgery [33,34]. These aberrations may seem trivial, but the planning and execution of surgery for sarcoma surgery are complex and highly dependent on the specific histological tumor type and its anatomical relationships to surrounding tissues in order to define the extent of resection required and the possible need for adjunctive reconstruction or space-filling procedures [35,36]. These considerations should be addressed at the outset of management, even before diagnostic sampling. A technically inadequate biopsy, particularly via a surgical approach, can have dramatic consequences with the risk of tumor dissemination into planes that are opened up to spread, making subsequent curative surgery more difficult or even impossible. For retroperitoneal STS, an international consensus conference consisting of the world's leading experts has now clearly defined the techniques for planning and performing an adequate surgical resection [36]. Several studies-have clearly shown that management of STS from the outset at a high patient-volume center of expertise led to improved local control in extremity sarcomas and

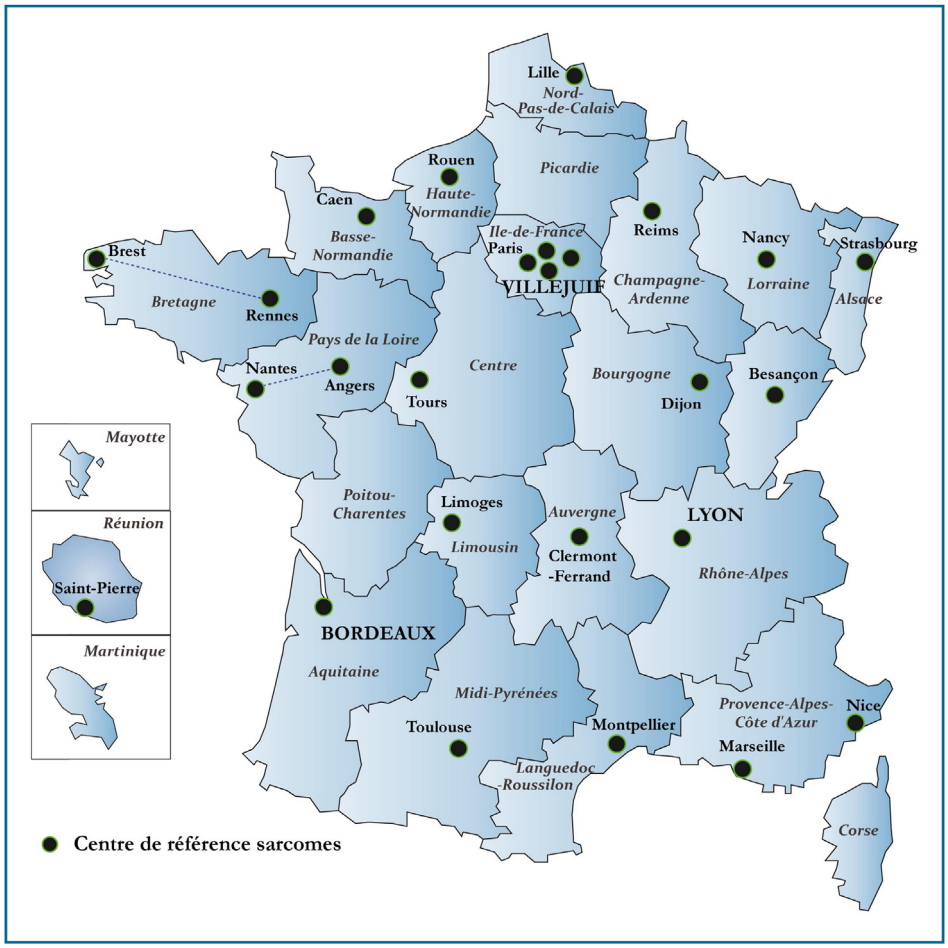

Figure 3. NetSarc clinical network (Sarcoma referral centers).

improved survival in thoracic or abdominal truncal sarcomas, and also that the shortcomings of an inadequate initial surgical could never be retrieved by subsequent treatments, no matter how aggressive [37—44]. A recent study showed that a patient who was not managed under the aegis of NetSarc was three times less likely to have his case discussed in a multidisciplinary conference, four times less likely to have adequate pre-operative imaging, and five times less likely to have a histologic diagnosis established prior to definitive surgery [34]. If established diagnostic and therapeutic recommendations are followed, a patient undergoing surgery for a retroperitoneal STS in France in 2014 has a 96-month median survival and a 54% 5-year disease-free survival [42]. Factors predictive for local recurrence were male sex, the invasion of an adjacent organ, intra-operative breach of the tumor, and non-expertise of the surgeon [42].

Recommendations for management

Starting in 2005, the ESMO has published recommendations that have been regularly updated to assure optimal management of sarcomas [33,45,46]. These recommendations can be summarized in three points:

- the need for appropriate initial imaging before treatment, i.e. CT for deep thoraco-abdominal STS, or MRI for parietal thoraco-abdominal, extremity, head or neck sarcomas;
- the need for co-axial percutaneous core needle biopsy under radiological control prior to any surgical treatment (en-bloc resection without tumor rupture is an alternative to percutaneous biopsy for adult patients with small superficial lesions < 5 cm);
- the need to refer any patient with an unexplained soft-tissue mass larger than 5 cm if superficial or of any size if deeply located to a center of expertise capable of providing a multidisciplinary approach. In France, this referral should be a center belonging to the RRePS or NetSarc networks.

Conclusions

Approximately 4000 new cases of STS are diagnosed each year in France. The development of the certified RRePS and NetSarc networks offers a structured approach to make a quasi-formal diagnosis of STS and to facilitate access to the necessary pathology, imaging and clinical tools to characterize the tumor, assess its scope, and arrange for appropriate medical and surgical treatment in a specialized center. These resources also allow dissemination of the culture of the multidisciplinary approach to management of STS and help to inform the medical community about the dangers of premature and inappropriate intervention decisions that are so often the source of treatment failure.

Key points

- There are more than 70 histological subtypes of sarcomas that can develop at any age, including childhood; these may occur at any anatomical location from head to toe.
- Four thousand new cases of STS are diagnosed each year in France, of which 23% are located in the abdominal area (abdominal organs, pelvis, retroperitoneum and abdominal wall).
- ESMO published recommendations for management of STS in 2005, which can be summarized in three points:
  - referral of any patient with an unexplained soft tissue mass (> 5 cm if superficial, or of any size if deep) to a center that can provide a multidisciplinary approach to management,
  - systematic performance of appropriate imaging prior to treatment (CT of deep thoraco-abdominal lesions or MRI for lesions of the thoraco-abdominal parietes, extremities, head or neck),
  - performance of co-axial percutaneous core needle biopsy under radiological control prior to any treatment. En bloc surgical resection without tumor violation is an alternative to percutaneous biopsy in adults if the lesion is superficial and <5 cm).
- The classification of an STS must consider the entirety of clinical information, such as patient age, tumor size and location; complete descriptive histological analysis according to the 2012 WHO classification, may be supplemented by molecular analysis where necessary; tumor aggressiveness should be evaluated by FNCLCC histological grade; tumor extent should be assessed by the TNM stage of the UICC and AJCC.
- When histological analysis is entrusted to a non-expert pathologist, the risk of initial diagnostic error is 10—25%; 4% of sarcomas will be mistaken for a benign lesion and 10% of benign lesions will be mistaken for sarcoma.
- The Reference Network for Pathology of Soft Tissue-GIST-Desmoid-Visceral Sarcomas (RRePS) is a grouping of expert pathologists certified by INCa whose goal is to offer a second reading of any new cases of STS or visceral sarcoma at no additional cost.
- The Clinical Reference Network for Sarcomas-GIST-Desmoids (NetSarc) is a group of practitioners certified for their expertise by the INCa whose aim is to define recommendations for management, to organize a referral structure for patient management, to coordinate research activities, to participate in epidemiological monitoring, and to set up a structured care pathway for patients and to implement physician training and continuing education.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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